REMARKS

This paper is in response to the non-final Office action mailed on October 16, 2007. Entry and consideration of this amendment is respectfully requested. This paper is accompanied by a petition for a one month extension of time and is thus timely filed.

I. Status of the Claims

Claims 1-3, 6-16, 18, 19, 23-27 are pending.

Claims 4, 5, 17, 20-22, and 25 are canceled without prejudice.

II. Amendments to the Claims

Claim 1 has been amended to modify the transitional phrase recited therein, and to delete certain language.

Claim 8 has been amended to differentiate from claim 1.

Claim 18 has been amended to conform to the language of newly amended claim 1.

Claim 19 has been amended to conform to the language of newly amended claim 1, and to recite covalent attachment of the water soluble polymer at a tyrosoine residue of the peptide. Support for this language is found, e.g., in Examples 5 and 6. Examples 5 and 6 describe PEGylation of DPDPE and biphalin, respectively. In examining the structures of each of these peptides (the structure of DPDPE is described in Example 6, while the structure of biphalin is provided in the specification at paragraph [0029]), along with the PEG reagent employed, it can be seen that conjugation of PEG is effected at the N-terminus (i.e., the amino group) of tyrosine. The activated PEG reagent employed, mPEG SPA (mPEG succinimidyl propionate), is a well-known electrophilically activated PEG that is reactive with amino groups such as those present on tyrosine. See, e.g., U.S. Patent No. 5,672,662 which describes mPEG SPA.

No new matter has been added to the claims by virtue of the amendments presented herein.

Although the present communication may include alterations to the claims and characterizations of claim scope or cited art, the Applicant is in no way conceding that previously pending claims are not patentable over the cited references or fail to comply with the requirements for patentability. Applicant reserves the right to pursue at a later date any previously pending or other broader or narrower claims that capture subject matter supported by the present disclosure, including subject matter that may have been disclaimed herein or by any prior prosecution directed to the subject matter described in the present disclosure.

III. Rejections under 35 U.S.C. §112, First Paragraph

The Examiner has rejected claims 1-3, 6-19, 23, 24, 26 and 27 under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. It is the Examiner's assertion that the subject claims contain subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention.

While in no way conceding to the Examiner's assertion, in particular in view of the field of the claims (chemistry), the transitional language employed, and the structure of the conjugates as claimed, Applicant has amended the claims to delete language objected to by the Examiner, strictly for the purposes of expediting prosecution.

In view of the amendment to the subject claims, it is submitted that the Examiner's rejection to the claims under 35 U.S.C. §112, first paragraph, has been overcome.

IV. Prior Art Rejections: Rejections Under 35 U.S.C. §103

A. GROUNDS OF REJECTION.

The Examiner has maintained the rejection of claims 1-3, 5-19, 21, 23, 26, and 27 under 35 U.S.C. §103(a) as unpatentable over Delgado, et al., and Wu, et al.

Specifically, the Examiner has maintained his position, that, based upon the teachings of Delgado and Wu, it would have been obvious at the time of the invention to arrive at a peptide that is either biphalin or DPDPE, covalently attached to a water

soluble polymer such as those recited in claim 1, to provide a hydrophilic conjugate capable of transport across the blood brain barrier when administered to the blood circulation.

This rejection is respectfully traversed for the reasons which follow, and those already of record.

B. THE CLAIMED INVENTION

The claims are directed to a hydrophilic polymer-peptide conjugate, which, when administered into the blood circulation of a mammal, is capable of transport across the blood brain barrier. The conjugate consists of:

(i) a peptide that is either biphalin or [D-Pen^2, D-Pen^5] enkephalin (DPDPE),

(ii) covalently linked to one or more water-soluble polymer chains having a molecular weight from about 2,000 to about 100,000 daltons and selected from either poly(ethylene glycol) or copolymers of ethylene glycol and propylene glycol.

The Examiner is reminded that the claims are not only directed to particular peptide-polymer conjugates, but also to conjugates capable *per se* of transport across the blood brain barrier – absent a transport vector of the type required by Wu, and further absent lipophilic moieties believed to facilitate transport of such peptides across the blood-brain barrier (BBB).

These features are believed to be a relevant factor in the "consideration of the invention as whole".

C. CITED ART

Delgado, et al. and Wu et al. have been extensively characterized in Applicant's prior Amendments, and such characterizations are not repeated here. The Examiner's attention is drawn to Applicant's Amendment dated November 17, 2006, which provides detailed characterization of both the Delgado and Wu references.

D. ARGUMENT

As reiterated by the Supreme Court in *KSR International Co. v. Teleflex, Inc.*, 82 USPQ2d 1385, 1391(2007), the framework that still controls an objective analysis for determining whether claims are obvious is stated in *Graham v. John Deere* Co., 383 U.S. 1, 148 USPQ 459 (1966). Specifically, the Graham factors include:

(i) Determining the scope and content of the prior art;

(ii) Ascertaining the differences between the claimed invention and the prior art; and

(iii) Resolving the level of ordinary skill in the pertinent art.

In applying the Graham factors, both the claimed invention and the references must be considered as a whole.

Finally, a prior art reference must be considered in its entirety, i.e., as a whole, *including portions that would lead away from the claimed invention. W.L. Gore & Associates, Inc. v. Garlock, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983).*

The real question to be considered in the instant analysis is the following: would one skilled in the art, having the Delgado and Wu references in hand, coupled with knowledge commonly available to one skilled in art, arrive at the invention embodied in the Applicant's claims? It is submitted that the answer to this question is no, for the reasons which follow.

1. Scope and Content of the Prior Art

Delgado is a 1992 review article describing several PEG-modified proteins, their pharmacological and chemical properties (antigenicity, renal clearance, bioactivity, etc.) in various systems, methods of synthesis and analyses, and the like.

Wu describes modification of brain-derived neurotrophic factor (BDNF) to provide a conjugate capable of transport across the BBB upon peripheral administration. The Wu conjugate employs the combined use of PEGylation technology (e.g., the PEG chains), chimeric peptide technology (e.g., the OX26 Mab), and avidin-biotin technology (e.g., the biotin-streptavidin, SA) (p. 254, column 2). Wu further describes the function

of each component of the BDNF conjugate. Wu describes the PEG chains as preventing rapid uptake of the protein by peripheral tissues, while the OX26 Mab functions as the transport vector which provides transport of the conjugate through the BBB, owing to high concentrations of the rat transferring receptor on the brain capillary endothelium. Conjugation of the PEG segment to the OX26 Mab is accomplished via a biotin/streptavidin complex. As Wu clearly describes, transport of the above three-component conjugate is facilitated by the OX26 Mab transport vector – not by the PEG.

2. Differences Between Art and Claims

Delgado fails to suggest a biphalin or a DPDPE PEG conjugate, let alone such a conjugate capable of administration to the bloodstream and transport across the BBB, and having an analgesic effect. Indeed, Delgado is not concerned with the problem of transport of small peptides across the blood-brain-barrier. Based upon the teachings of Wu, there is absolutely no reason to modify Wu in view of Delgado to arrive at the Applicant's claimed conjugate, since one would expect, based upon Wu, such modifications to yield a conjugate incapable of transport across the blood brain barrier.

Wu is directed to neutrophic factors such as BDNF, a protein produced from a nucleotide sequence over 4000 nucleotides in length. In contrast, the claimed peptides are *small peptides* – not large proteins such as BDNF. Biphalin is a dimer made up of eight amino acids, while DPDPE possesses the structure, Tyr-D-Pen-Gly-Phe-D-Pen (where Pen refers to penicillamine). Nowhere does Wu suggest small peptides, let alone biphalin or DPDPE, nor does Wu suggest anything other than a combination of PEGylation and attachment of a drug delivery system such as OX26 Mab to BDNF to provide transport across the BBB.

Nowhere does Wu describe or even remotely suggest preparing a BDNF or any other sort of conjugate where BDNF is conjugated merely to PEG, for transport across the blood brain barrier or for any other purpose. Indeed, on page 257, column 1, Wu states that in order to demonstrate therapeutic efficacy, BDNF *must be* (i) conjugated to a BBB drug delivery system (i.e., OX26 Mab), and (ii) PEGylated to improve plasma pharmacokinetics.

To modify Wu to arrive at a conjugate of the present invention would be to go against the very teachings of Wu – by eliminating a feature described by Wu as essential to the invention (i.e., the transport vector). In fact, Wu states on page 257, column 2, that monobiotinylation and placement of biotin are *critical factors* involved in enabling transport of BDNF across the BBB (second and third full paragraphs).

3. Resolving the level of ordinary skill in the pertinent art

The Applicant respectfully submits that the Examiner is ignoring one feature of the invention – the surprising ability of the recited conjugates to cross the blood brain barrier. While the review article of Delgado does indeed address the benefits of PEGylation of proteins, the instant claims have nothing to do with proteins, but rather, are concerned with biphalin and DPDPE, and the problem of transport of such compounds across the blood brain barrier.

In further support of the level of skill in the art, enclosed herewith are two additional articles, both of which speak to the difficulties in delivering drugs across the blood brain barrier.

Jeffrey, S., in *"Manipulating the Blood-Brain Barrier – A Realistic Therapeutic Goal?*, Neurology Review.Com, Clinical trends and news in neurology (Vol. 8, No. 7, July, 2000), describes the difficulties for gaining drug access to the brain. Strategies for access into the brain are described to include the use of small, lipophilic compounds, receptor-mediated endocytosis, transport proteins, and the use of viral vectors.

Bryan, Jenny, in a publication several years after the claimed invention, entitled *"Crossing the blood brain barrier: drug delivery to the brain is still elusive"*, The Pharmaceutical Journal, Vol. 273, October 2004), describes the challenges with formulating drugs capable of transport across the blood brain barrier. Bryan reiterates the view that uncharged, lipophilic compounds are considered as having the greatest chance of crossing the blood brain barrier, and reviews various efforts to manipulate or transport the blood brain barrier.

In sum, the state of the art at the time of the claimed invention (and even after) views the transport of compounds across the blood brain barrier as an elusive challenge. Moreover, if anything, the state of the art points to the need for either an

active transport system (such as nanoparticles, liposomes, vectors) or synthetic chemistry approaches for arriving at a compound capable of transport across the blood brain barrier.

4. Analysis: The Combination of References Fails to Yield Predictable Results When Considering the References and the Claims as a Whole, in View of the State of the Art at the Time of the Invention.

"The test for an implicit showing is what the combined teachings, knowledge of one of ordinary skill in the art, and the nature of the problem to solved as a whole would have suggested to those of ordinary skill in the art." *In re Kotzab*, 217 F.3d 1365, 1370, 55 USPQ 1313, 1317 (Fed. Cir. 2000), *In re Lee*, 277 F.3d 1338, 1342-44, 61 USPQ2d 1430, 1433-34.

It is submitted that the Examiner is arbitrarily combining the references Wu and Delgado to support an assertion that the claims are obvious – without any consideration of what each of the references (when considered along with the state of the art at the time of the invention) actually teaches when considered *as a whole*.

a. At the time of the instant invention, is was generally believed that compounds that were non-lipophilic and had a molecular weight greater than about 500 daltons generally did not cross the blood-brain barrier (specification, page 1, paragraph [004]).

b. The review articles provided by the Applicant further point to the difficulties of drug transport across the blood brain barrier, and the need for transport systems and the like.

c. Wu teaches away from the claimed conjugates in stating that the transport vector described therein is essential to transport across the blood brain barrier.

d. In view of the foregoing, the combination relied upon by the Examiner fails to yield predictable results. That is to say, the ability of the claimed conjugate to cross the blood brain barrier is completely unexpected in view of the art.

In view of the above, it is submitted that the pending claims are non-obvious and comply with the standards of 35 U.S.C. §103. Withdrawal of the rejection of the claims under 35 U.S.C. §103 is therefore respectfully requested.

V. List of Copending Applications

The Examiner has requested a list of all copending applications that set forth similar subject matter to the present claims, in addition to copies of any such copending claims.

The Examiner's attention is drawn to Applicant's Amendment dated May 22, 2006 in which two related pending applications were identified: U.S. Application No. 10/354,879 (now abandoned) and U.S. Application No. 10/354,683. The claims currently pending in U.S. Application No. 10/354,683 are appended to this communication.

VI. Conclusion

In view of the foregoing, the Applicant submits that all of the claims pending in the application patentably define over the cited art and meet the requirements of 35 U.S.C. §112. A Notice of Allowance is therefore respectfully requested.

If a telephone conference would expedite the prosecution of the subject application, the Examiner is requested to call the undersigned at (650) 838-4406.

Respectfully submitted,
Perkins Coie LLP

Date: February 15, 2008

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CLAIMS PENDING IN APPLICATION NO.: 10/354,683
EXAMINER Cordero Garcia, M. M.,
Entitled: POLYMER STABILIZED NEUROPEPTIDES

Claims 1-26. (Canceled).

27. (Previously Presented). A method for delivering an opioid peptide into the brain of a mammal through the blood-brain barrier, said method comprising: administering into the blood stream of said mammal a substantially hydrophilic conjugate comprising an opioid peptide covalently attached to a hydrophilic water-soluble polymer, to thereby transport said conjugate across the blood brain barrier of said mammal, wherein (i) said opioid peptide is selected from the group consisting of dynorphins, enkephalins, an enkephalin analog that is either biphalin or [D-Pen^2,D-Pen^5]enkephalin (DPDPE), endorphins, and endomorphins, and (ii) said hydrophilic water-soluble polymer is either a polyethylene glycol or a copolymer of polyethylene glycol and polypropylene glycol, having a nominal average molecular weight of about 200 daltons to about 40,000 daltons.

28. (Previously Presented) The method of Claim 27, wherein said conjugate further comprises doxorubicin or fluoroscein covalently attached to said hydrophilic water-soluble polymer.

29. (Previously Presented) The method of Claim 27, wherein said conjugate further comprises doxorubicin covalently attached to said hydrophilic water-soluble polymer.

30. (Previously Presented). The method of Claim 27, wherein said conjugate further comprises a neuroactive agent which may be the same or different from said opioid peptide covalently attached to said hydrophilic water-soluble polymer.

31. (Previously Presented) The method of Claim 27, wherein the polymer is selected from the group consisting of monomethoxypolyethylene glycol, branched polyethylene glycol, polyethylene glycol with degradable linkages in the backbone, homobifunctional polyethylene glycol, heterobifunctional polyethylene glycol, multi-arm

polyethylene glycol, pendant polyethylene glycol, and forked polyethylene glycol.

32. (Previously Presented) The method of Claim 31, wherein the polymer has a nominal average molecular weight from about 300 to about 8,000 Daltons.

33. (Previously Presented) The method of Claim 27, wherein the opioid peptide is either biphalin or DPDPE.

34. ((Previously Presented) The method of Claim 28, wherein the polymer is a linear polymer having a first terminus covalently attached to said opioid peptide and a second terminus covalently attached to doxorubicin or fluoroscein.

35. (Previously Presented) The method of Claim 27, wherein said administering comprises parenteral administration.

36. (Previously Presented) The method of Claim 27, wherein said administering comprises either pulmonary or intranasal inhalation.

37. (Previously Presented) The method of Claim 27, wherein said administering is by a route selected from the group consisting of oral, ocular, buccal, transdermal, pulmonary, and rectal administration.

38 - 40. (Canceled)

41. (Previously Presented) The method of Claim 27, wherein the opioid peptide is DPDPE.

42. (Withdrawn) The method of Claim 39 wherein the peptide is biphalin.

43. (Canceled)

44. (Previously Presented) The method of Claim 27 wherein the conjugate is administered by a route selected from the group consisting of intravenous injection, subcutaneous injection, parenteral injection, and intramuscular injection.

45 - 54. (Canceled)

55. ((Previously Presented). The method of claim 27, wherein said mammal is a human.

56. (Previously Presented). The method of claim 27, wherein the polyethylene glycol polymer or copolymer has a nominal average molecular weight from about 2000 to 20,000 Daltons.

57. (New) The method of claim 27, whereby as a further result of said administering, said conjugate provides an analgesic effect in said mammal.

58. (New) The method of claim 31, wherein the polymer is monomethoxypolyethylene glycol.

59. (New) The method of claim 27, wherein said opioid peptide is covalently attached to a single hydrophilic water-soluble polymer.

60. (New) The method of claim 27, wherein said opioid peptide is covalently attached to two hydrophilic water-soluble polymer chains.

61. (New) The method of claim 27, wherein said administering comprises administering said substantially hydrophilic conjugate in combination with a pharmaceutically acceptable carrier.

62. (New) The method of Claim 31, wherein the polymer has a nominal average molecular weight from about 500 to about 5,000 Daltons.